PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
339240/17061		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 98/01193	17/07/1998	18/07/1997
Applicant		
GENSET et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readble form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 98/01193

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 111
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 111 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

127,129 (partial); 1-126,131,138 (complete)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 127,129 (partial); 1-126,131,138 (complete)

An isolated nucleic acid comprising a biallelic marker sequence selected from the group of SEQ ID NO:301, SEQ ID NO:307, their complementary sequences, or fragments comprising at least 8 consecutive nucleotides including the biallelic marker site,
a set of nucleic acids including such biallelic markers, methods of obtaining such a set, arrays of nucleic acids comprising such a set, a map comprising such an array, methods of identifying biallelic markers associated with a detectable trait or an individual's risk of developing such a trait, methods of identifying a gene or a haplotype associated with such a trait, a method of selecting an individual for a treatment, a method of treatment of such an individual, and a method of determining an individual's risk of developing or possessing Alzheimer's disease.

2. Claims: 127,129 (partial); 132 (complete)

An isolated nucleic acid comprising a biallelic marker sequence selected from the group of SEQ ID NO:302, SEQ ID NO:308, their complementary sequences, or fragments comprising at least 8 consecutive nucleotides including the biallelic marker site, and a method of determining an individual's risk of developing or possessing Alzheimer's disease.

3. Claims: 127,129 (partial); 133 (complete)

An isolated nucleic acid comprising a biallelic marker sequence selected from the group of SEQ ID NO:303, SEQ ID NO:309, their complementary sequences, or fragments comprising at least 8 consecutive nucleotides including the biallelic marker site, and a method of determining an individual's risk of developing or possessing Alzheimer's disease.

4. Claims: 127,129 (partial); 134 (complete)

An isolated nucleic acid comprising a biallelic marker sequence selected from the group of SEQ ID NO:304, SEQ ID NO:310, their complementary sequences, or fragments comprising at least 8 consecutive nucleotides including the biallelic marker site, and a method of determining an individual's risk of developing or possessing Alzheimer's disease.

5. Claims: 127,129 (partial); 135 (complete)

An isolated nucleic acid comprising a biallelic marker

sequence selected from the group of SEQ ID NO:305, SEQ ID NO:311, their complementary sequences, or fragments comprising at least 8 consecutive nucleotides including the biallelic marker site, and a method of determining an individual's risk of developing or possessing Alzheimer's disease.

6. Claims: 127 (partial); 128,130 (complete)

An isolated nucleic acid comprising a biallelic marker sequence selected from SEQ ID NO:306, its complementary sequence, or fragments comprising at least 8 consecutive nucleotides including the biallelic marker site, and a method of determining an individual's risk of developing or possessing Alzheimer's disease.

7. Claims: 136,139 (complete)

An isolated nucleic acid primer for amplification selected from the group of SEQ ID Nos:313-317 and SEQ ID Nos:319-323, their complementary sequences, or fragments comprising at least 8 consecutive nucleotides, and a set of nucleic acids comprising such a primer.

8. Claims: 137,140 (complete)

An isolated nucleic acid primer for microsequencing selected from the group of SEQ ID Nos:325-329 and SEQ ID Nos:331-335, their complementary sequences, or fragments comprising at least 8 consecutive nucleotides, and a set of nucleic acids comprising such a primer.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 98/01193

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 12607 A (MOLECULAR TOOL INC) 11 May 1995	1,14,20, 24-28, 36, 47-51, 61-67, 78-80, 107,108, 117-122, 138
Y	see the whole document	22,23, 52-55, 123-126
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 1999	22. 04. 1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Knehr, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG D ET AL: "Towards a third generation genetic map of the human genome based on biallelic polymorphisms." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 59, 1996, page A3 XP002050641	1,14-16, 24-28, 36, 47-51, 81-84, 93, 104-106, 138
Y	see abstract	52-60, 85-92, 94-103
X	WO 91 13075 A (ORION YHTYMAE OY) 5 September 1991	48-51, 107,108, 127
	see the whole document	
Y	KIM UJ ET AL: "Construction and characterization of a human bacterial artificial chromosome library" GENOMICS, vol. 34, 1996, pages 213-218, XP002050639 cited in the application see the whole document	1,22
Y	CHEE M ET AL: "Assessing genetic information with high-density DNA arrays" SCIENCE, vol. 274, 1996, pages 610-614, XP002050640 see the whole document	85-92, 94-103, 123-126
Y	COX DR ET AL: "Assessing mapping progress in the human genome project" SCIENCE, vol. 265, 1994, pages 2031-2032, XP002050642 see the whole document	1,23, 55-60
A	HUDSON TJ ET AL: "An STS-based map of the human genome" SCIENCE, vol. 270, 1995, pages 1945-1954, XP002050645 cited in the application see the whole document	
A	SCHULER GD ET AL: "A gene map of the human genome" SCIENCE, vol. 274, 1996, pages 540-546, XP002050646 cited in the application see the whole document	

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 98/01193

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	FAN J ET AL.: "Genetic mapping: Finding and analyzing single-nucleotide polymorphisms with high-density DNA arrays" AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 4 Suppl., 1997, page 1601 XP002089397 see abstract ---	1,14-16, 20-31, 36-51, 55, 81-85, 93-106, 138
P,X	WANG D G ET AL.: "Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome." SCIENCE, vol. 280, 1998, pages 1077-1082, XP002089398 see the whole document ---	1,14, 20-32, 36-51, 81-84, 93,138
P,X	KRUGLYAK L: "The use of a genetic map of biallelic markers in linkage studies" NATURE GENETICS, vol. 17, no. 1, 1997, pages 21-24, XP002050647 see the whole document ---	1,14, 20-28, 36, 47-51, 61-67, 78-84, 93,94, 107,108, 117-123, 138
P,X	EP 0 785 280 A (AFFYMETRIX INC) 23 July 1997 see the whole document ---	1,47,48, 81-83, 89-91
P,X	SCHORK N J ET AL.: "Linkage disequilibrium mapping for quantitative traits within case/control settings." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 4 Suppl., 1997, page A293 XP002089399 see abstract -----	1,27,28, 48-51, 55-60, 138

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 98/01193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9512607 A	11-05-1995	AU 8132194 A	23-05-1995
		CA 2175695 A	11-05-1995
		EP 0726905 A	21-08-1996
		US 5762876 A	09-06-1998
WO 9113075 A	05-09-1991	AU 642709 B	28-10-1993
		AU 7235191 A	18-09-1991
		CA 2071537 A	17-08-1991
		DE 648280 T	30-11-1995
		EP 0648280 A	19-04-1995
		ES 2072235 T	16-07-1995
		FI 923653 A	14-08-1992
		GR 95300047 T	31-07-1995
		HU 211058 B	30-10-1995
		IL 97222 A	31-08-1995
		JP 2786011 B	13-08-1998
		JP 5504477 T	15-07-1993
		PT 96776 A,B	31-10-1991
EP 0785280 A	23-07-1997	US 5858659 A	12-01-1999

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 April 1999 (27.04.99)	
International application No. PCT/IB98/01193	**Applicant's or agent's file reference** 339240/17061
International filing date (day/month/year) 17 July 1998 (17.07.98)	**Priority date** (day/month/year) 18 July 1997 (18.07.97)
Applicant COHEN, Daniel et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 February 1999 (15.02.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
339240/17061		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB98/01193	17/07/1998	18/07/1997
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant GENSET et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/02/1999	28. 10. 99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stricker, J-E Telephone No. +49 89 2399 8395

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB98/01193

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-88	as originally filed

Claims, No.:

1-85	as received on	07/10/1999	with letter of	06/10/1999

Drawings, sheets:

1/16-16/16	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 58-60; 73 and 75 (partial); 74, 76, 78-85 (complete).

because:

☒ the said international application, or the said claims Nos. 58-60, regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 73 and 75 (partial); 74, 76, 78-85 (complete).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	58-63, 73, 75, 77
	No:	Claims	37, 38, 41-45, 49-51, 53-57, 64-68
Inventive step (IS)	Yes:	Claims	58-63, 73, 75, 77
	No:	Claims	1-57, 64-72
Industrial applicability (IA)	Yes:	Claims	1-57, 61-73, 75, 77
	No:	Claims	-

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III

Claims 58-60 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

Reference is made to the following documents:

D1: WO 95 12607 A

D2: WANG D ET AL: 'Towards a third generation genetic map of the human genome based on biallelic polymorphisms.' AMERICAN JOURNAL OF HUMAN GENETICS, vol. 59, 1996, page A3.

D3: WO 91 13075 A

D4: CHEE M ET AL: 'Assessing genetic information with high-density DNA arrays' SCIENCE, vol. 274, 1996, pages 610-614.

D5: COX DR ET AL: 'Assessing mapping progress in the human genome project' SCIENCE, vol. 265, 1994, pages 2031-2032.

1. D1 discloses a method for identifying single nucleotide polymorphism (SNP) sites in the genome of animals (p.16-18 and claim 30) which are in fact biallelic markers (p.10). A random library has been used and cloning has been performed (p.16-17 and example 1). The creation of a map is presented (claim 25), thus the said markers have been ordered and their exact positions have been determined (table 5 on p.59, which shows a set of biallelic markers). The prediction of the exhibition of a particular trait by using biallelic markers is disclosed (p.42-44 and claims 20, 28). The association of biallelic markers with some particular traits, like diseases, can been achieved (p.13, 36, 37, 42-44). Alleles that do not segregate randomly

can be used for that purpose (p.42, l.19). The plurality of biallelic markers obtained by the method of claim 1 would appear to encompass those identified in D1.

D1 is therefore prejudicial to the novelty of the following **claims: 37, 38, 41-43, 55-57, 64-68** (Art. 33(2) PCT).

The subject-matter of claim 1 differs from this known method in that the order of the genomic DNA fragments in the genome is determined. The subject-matter of claim 1 is therefore novel (Article 33(2) PCT).

The problem to be solved by the present invention may therefore be regarded as how to provide an alternative method of obtaining a plurality of biallelic markers. The solution proposed in **Claim 1** of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) because the skilled person would regard it a normal design procedure to combine all the features set out in the said claim, in particular when a map comprising several thousands of markers is desired (cf. D2, last paragraph, combined with the teaching of D1, especially p.43, l.17-23).

Dependent **claims 2-26** do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to inventive step (Art. 33(3) PCT).

2. D2 discloses the construction of a third generation map of the human genome based on biallelic polymorphism. The subject-matter of **claim 27** differs in that the markers are on average evenly spaced over the full genome or a portion thereof and thus would appear to be novel (Art. 33(2) PCT. However, since this feature is already suggested in D2 (cf. last paragraph), the subject-matter of **claims 27-29** would not appear to involve an inventive step (Art. 33(2) PCT).

3. D3 (cf. abstract) describes a method for identifying specific point mutations (SNP). The ordered SNP sites, which are disclosed in the examples (p.20-45), are in fact biallelic markers which could have been identified by the method of claims 1, 37 or 42 of the present application. A method of detecting a predisposition to a genetic

disorder resulting from a SNP is disclosed in claim 3.

D3 is therefore prejudicial to the novelty of **claims: 55-57** (Art. 33(2) PCT).

4. D4 discloses the use of DNA arrays containing up to 135.000 probes complementary to the 16.6 kb human mitochondrial genome for identifying SNP sites (abstract and p.613). It is clear from the results shown in Figs. 1a and 3 that nucleic acids including a polymorphic nucleotide are present on the array.

   Thus, **claims 44, 45, 49-51, 53, 54** do not meet the requirements of Art. 33(2) PCT.

5. A map being the subject-matter of claim 36 has not been disclosed in the known prior art. In view of D2, the problem to be solved can be regarded as the provision of a map comprising an ordered array of a larger number of biallelic markers.
   D2 suggests that a genetic map consisting of 2000 SNPs should be sufficient for comprehensive coverage in genetic mapping studies. However, since a) the human genome is 3.10^9 bp long, b) its entire coding content is estimated at 100,000 genes, c) SNPs appear to occur at a rate of at least 1/1000 bp (D2), and d) a map of the human genome with 100 kb average resolution is desired (D5, last paragraph), in order to solve the problem posed, the skilled person would be motivated to identify and map a higher number of biallelic markers.
   Thus, the subject-matter **claim 36** would not appear to involve an inventive step (Art. 33(3) PCT).

6. D1 describes a method which involves the characterization of SNPs by using immobilized amplification primers (cf. claim 16). In order to compare or identify several SNP sites at the same time (see e.g. D4), it would be obvious for the skilled person to provide an array of the said primers. The further incorporation of several nucleotides (e.g. at least 8 nucleotides) or a single one (as in D1) would not appear to affect the composition of the said array.
   In D3, amplification products are immobilized via the corresponding primers (cf. p.10-13). Alternatively, it would be obvious to the skilled person that the primers could have been immobilized first.
   Similar arguments would apply to microsequencing primers, which were known in

the art (cf. D1, p.46, l.5-10).

Thus, the subject-matter of independent **claims 46, 47 and 48** would not appear to involve an inventive step (Art. 33(3) PCT).

7. The known prior art neither discloses nor renders obvious the subject-matter of independent **claims 58 and 61**, which therefore meets the requirements of Art. 33(2) and (3) PCT. **Claims 59, 60, 62 and 63** are dependent on the said claims and as such also meet the requirements of the PCT with respect to novelty and inventive step.

For the assessment of the present **claims 58-60** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

8. The identification of a haplotype associated with a trait is already suggested in the prior art (cf. e.g. D1, supra), thus the steps consisting of "obtaining nucleic acids samples from trait positive and trait negative individuals", "determining the identities of the polymorphic bases [...]" and further "identifying a haplotype having statistically significant association with said trait" which are common to claims 69-72 would obviously belong to such a method.
Therefore, the problem to be solved may be regarded as "how to determine the said polymorphic bases".

One solution to this problem is disclosed in D4 (supra). Adding a preceding amplification step is common in the art. Since it would be obvious for the skilled person to combine the above-mentioned teaching of D1 with the knowledge of D4, the subject-matter of **claim 69** does not appear to involve an inventive step (Art. 33(3) PCT).

Microsequencing used for the purpose of the present application is known in the

art (see D1 and D3 supra). In view of the known advantages provided by solid phase sequencing, it would be obvious for the skilled person to contemplate combining all the features set out in **claims 70 and 71**. Thus the latter do not appear to involve an inventive step as required by Art. 33(3) PCT.

In view of item 3 above, fore-last sentence, and the knowledge in solid phase sequencing available in the art (see p.50, l.3-5 of the present application), the subject-matter of **claim 72** does not meet the requirements of Art. 33(3) PCT.

9. The subject-matter of **claim 73** differs from the teaching of D3 in that the polymorphism located in SEQ ID Nos: 301 and 307 (A allele and G allele of marker 99-344/439, respectively) is not disclosed. Thus, it meets the requirements of Art. 33(2) PCT.
Since no document from the known prior art renders obvious it's association with Alzheimer's Disease (AD), the subject-matter of claim 127 can be considered as involving an inventive step (Art. 33(3) PCT). However, see also item 1 in section VIII below.

Claim 75 (regarding SEQ ID Nos: 301, 307 and 311 only) is dependent on claim 73 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

10. Since SEQ ID No. : 301 and 307, and fragments thereof comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, are neither disclosed in -nor rendered obvious by- the known prior art, the subject-matter of **claim 77** meets the requirements of the PCT with respect to novelty and inventive step (Art. 33(2) and (3) PCT).

11. Dependent **claims 30-35, 39, 40, 52** do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to inventive step (Art. 33(3) PCT).

12. If the claimed priority date is not valid, the following documents may be relevant:

FAN J ET AL.: 'Genetic mapping: Finding and analyzing single-nucleotide polymorphisms with high-density DNA arrays' AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 4

Suppl., 1997, page 1601.

WANG D G ET AL.: 'Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome.' SCIENCE, vol. 280, 1998, pages 1077-1082.

KRUGLYAK L: 'The use of a genetic map of biallelic markers in linkage studies' NATURE GENETICS, vol. 17, no. 1, 1997, pages 21-24.

SCHORK N J ET AL.: 'Linkage disequilibrium mapping for quantitative traits within case/control settings.' AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 4 Suppl., 1997, page A293.

Section VI

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
EP-A-0 785 280	23.07.1997	28.11.1996	29.11.1995*

* The validity of the claimed priority date has not been checked.

Section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D5 is not mentioned in the description, nor are these documents identified therein.

Section VIII

1. According to the results presented on p.37 (table 3) and the comments on p.46, l.10-11, the determination of the SNP within SEQ ID No. : 301/307 does not seem

to be sufficient to determine whether a patient is at risk of developing - or suffers from- AD. Either the determination of the "haplotype 8" (see fig.7) or the SNP within SEQ ID No. : 304/310 (biallelic marker 99-365/344) seems to be necessary (see p.47, l.1-12). Therefore it would appear that some essential features are missing from **claim 73** (Article 6 taken in combination with Rule 6.3(b) PCT).

2. The method of **claim 55** refers to biallelic markers obtained by the method of claim 1, however the latter are not associated with a trait. Therefore the said claim is not clear (Art. 6 PCT).

3. The expression "known to be located in proximity to one another in the genome" to be found in **several claims** is not clear (Art. 6 PCT) because the term "proximity" is vague and unclear.

4. **Claims 1-72** do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

5. **Claims 1-72** would appear to be not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following: the said claims concern biallelic markers and their use, however the description appears to refer to biallelic markers that consist of SNPs, and the use thereof.

PATENT COOPERATION TREATY

HIP

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MARTIN, J.
Cabinet REGIMBEAU
26, avenue Kléber
75116 Paris
FRANCE

ARRIVE LE
- 2 NOV. 1999
CABINET
REGIMBEAU

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	28. 10. 99
Applicant's or agent's file reference 339240/17061	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB98/01193	17/07/1998	18/07/1997

Applicant
GENSET et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the International preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
339240/17061		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IB98/01193	17/07/1998	18/07/1997
International Patent Classification (IPC) or national classification and IPC		
C12Q1/68		
Applicant		
GENSET et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/02/1999	28.10.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stricker, J-E Telephone No. +49 89 2399 8395

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB98/01193

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-88 as originally filed

Claims, No.:

1-85 as received on 07/10/1999 with letter of 06/10/1999

Drawings, sheets:

1/16-16/16 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 58-60; 73 and 75 (partial); 74, 76, 78-85 (complete).

because:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB98/01193

☒ the said international application, or the said claims Nos. 58-60, regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 73 and 75 (partial); 74, 76, 78-85 (complete).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	58-63, 73, 75, 77
	No:	Claims	37, 38, 41-45, 49-51, 53-57, 64-68
Inventive step (IS)	Yes:	Claims	58-63, 73, 75, 77
	No:	Claims	1-57, 64-72
Industrial applicability (IA)	Yes:	Claims	1-57, 61-73, 75, 77
	No:	Claims	-

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III

Claims 58-60 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

Reference is made to the following documents:

D1: WO 95 12607 A

D2: WANG D ET AL: 'Towards a third generation genetic map of the human genome based on biallelic polymorphisms.' AMERICAN JOURNAL OF HUMAN GENETICS, vol. 59, 1996, page A3.

D3: WO 91 13075 A

D4: CHEE M ET AL: 'Assessing genetic information with high-density DNA arrays' SCIENCE, vol. 274, 1996, pages 610-614.

D5: COX DR ET AL: 'Assessing mapping progress in the human genome project' SCIENCE, vol. 265, 1994, pages 2031-2032.

1. D1 discloses a method for identifying single nucleotide polymorphism (SNP) sites in the genome of animals (p.16-18 and claim 30) which are in fact biallelic markers (p.10). A random library has been used and cloning has been performed (p.16-17 and example 1). The creation of a map is presented (claim 25), thus the said markers have been ordered and their exact positions have been determined (table 5 on p.59, which shows a set of biallelic markers). The prediction of the exhibition of a particular trait by using biallelic markers is disclosed (p.42-44 and claims 20, 28). The association of biallelic markers with some particular traits, like diseases, can been achieved (p.13, 36, 37, 42-44). Alleles that do not segregate randomly

can be used for that purpose (p.42, l.19). The plurality of biallelic markers obtained by the method of claim 1 would appear to encompass those identified in D1.

D1 is therefore prejudicial to the novelty of the following **claims: 37, 38, 41-43, 55-57, 64-68** (Art. 33(2) PCT).

The subject-matter of claim 1 differs from this known method in that the order of the genomic DNA fragments in the genome is determined. The subject-matter of claim 1 is therefore novel (Article 33(2) PCT).

The problem to be solved by the present invention may therefore be regarded as how to provide an alternative method of obtaining a plurality of biallelic markers. The solution proposed in **Claim 1** of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) because the skilled person would regard it a normal design procedure to combine all the features set out in the said claim, in particular when a map comprising several thousands of markers is desired (cf. D2, last paragraph, combined with the teaching of D1, especially p.43, l.17-23).

Dependent **claims 2-26** do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to inventive step (Art. 33(3) PCT).

2. D2 discloses the construction of a third generation map of the human genome based on biallelic polymorphism. The subject-matter of **claim 27** differs in that the markers are on average evenly spaced over the full genome or a portion thereof and thus would appear to be novel (Art. 33(2) PCT. However, since this feature is already suggested in D2 (cf. last paragraph), the subject-matter of **claims 27-29** would not appear to involve an inventive step (Art. 33(2) PCT).

3. D3 (cf. abstract) describes a method for identifying specific point mutations (SNP). The ordered SNP sites, which are disclosed in the examples (p.20-45), are in fact biallelic markers which could have been identified by the method of claims 1, 37 or 42 of the present application. A method of detecting a predisposition to a genetic

disorder resulting from a SNP is disclosed in claim 3.

D3 is therefore prejudicial to the novelty of **claims: 55-57** (Art. 33(2) PCT).

4. D4 discloses the use of DNA arrays containing up to 135.000 probes complementary to the 16.6 kb human mitochondrial genome for identifying SNP sites (abstract and p.613). It is clear from the results shown in Figs. 1a and 3 that nucleic acids including a polymorphic nucleotide are present on the array.

Thus, **claims 44, 45, 49-51, 53, 54** do not meet the requirements of Art. 33(2) PCT.

5. A map being the subject-matter of claim 36 has not been disclosed in the known prior art. In view of D2, the problem to be solved can be regarded as the provision of a map comprising an ordered array of a larger number of biallelic markers. D2 suggests that a genetic map consisting of 2000 SNPs should be sufficient for comprehensive coverage in genetic mapping studies. However, since a) the human genome is 3.10^9 bp long, b) its entire coding content is estimated at 100,000 genes, c) SNPs appear to occur at a rate of at least 1/1000 bp (D2), and d) a map of the human genome with 100 kb average resolution is desired (D5, last paragraph), in order to solve the problem posed, the skilled person would be motivated to identify and map a higher number of biallelic markers.
Thus, the subject-matter **claim 36** would not appear to involve an inventive step (Art. 33(3) PCT).

6. D1 describes a method which involves the characterization of SNPs by using immobilized amplification primers (cf. claim 16). In order to compare or identify several SNP sites at the same time (see e.g. D4), it would be obvious for the skilled person to provide an array of the said primers. The further incorporation of several nucleotides (e.g. at least 8 nucleotides) or a single one (as in D1) would not appear to affect the composition of the said array.
In D3, amplification products are immobilized via the corresponding primers (cf. p.10-13). Alternatively, it would be obvious to the skilled person that the primers could have been immobilized first.
Similar arguments would apply to microsequencing primers, which were known in

the art (cf. D1, p.46, l.5-10).

Thus, the subject-matter of independent **claims 46, 47 and 48** would not appear to involve an inventive step (Art. 33(3) PCT).

7. The known prior art neither discloses nor renders obvious the subject-matter of independent **claims 58 and 61**, which therefore meets the requirements of Art. 33(2) and (3) PCT. **Claims 59, 60, 62 and 63** are dependent on the said claims and as such also meet the requirements of the PCT with respect to novelty and inventive step.

For the assessment of the present **claims 58-60** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

8. The identification of a haplotype associated with a trait is already suggested in the prior art (cf. e.g. D1, supra), thus the steps consisting of "obtaining nucleic acids samples from trait positive and trait negative individuals", "determining the identities of the polymorphic bases [...]" and further "identifying a haplotype having statistically significant association with said trait" which are common to claims 69-72 would obviously belong to such a method.
Therefore, the problem to be solved may be regarded as "how to determine the said polymorphic bases".

One solution to this problem is disclosed in D4 (supra). Adding a preceding amplification step is common in the art. Since it would be obvious for the skilled person to combine the above-mentioned teaching of D1 with the knowledge of D4, the subject-matter of **claim 69** does not appear to involve an inventive step (Art. 33(3) PCT).

Microsequencing used for the purpose of the present application is known in the

art (see D1 and D3 supra). In view of the known advantages provided by solid phase sequencing, it would be obvious for the skilled person to contemplate combining all the features set out in **claims 70 and 71**. Thus the latter do not appear to involve an inventive step as required by Art. 33(3) PCT.

In view of item 3 above, fore-last sentence, and the knowledge in solid phase sequencing available in the art (see p.50, l.3-5 of the present application), the subject-matter of **claim 72** does not meet the requirements of Art. 33(3) PCT.

9. The subject-matter of **claim 73** differs from the teaching of D3 in that the polymorphism located in SEQ ID Nos: 301 and 307 (A allele and G allele of marker 99-344/439, respectively) is not disclosed. Thus, it meets the requirements of Art. 33(2) PCT.
Since no document from the known prior art renders obvious it's association with Alzheimer's Disease (AD), the subject-matter of claim 127 can be considered as involving an inventive step (Art. 33(3) PCT). However, see also item 1 in section VIII below.

Claim 75 (regarding SEQ ID Nos: 301, 307 and 311 only) is dependent on claim 73 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

10. Since SEQ ID No. : 301 and 307, and fragments thereof comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, are neither disclosed in -nor rendered obvious by- the known prior art, the subject-matter of **claim 77** meets the requirements of the PCT with respect to novelty and inventive step (Art. 33(2) and (3) PCT).

11. Dependent **claims 30-35, 39, 40, 52** do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to inventive step (Art. 33(3) PCT).

12. If the claimed priority date is not valid, the following documents may be relevant:

FAN J ET AL.: 'Genetic mapping: Finding and analyzing single-nucleotide polymorphisms with high-density DNA arrays' AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 4

Suppl., 1997, page 1601.

WANG D G ET AL.: 'Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome.' SCIENCE, vol. 280, 1998, pages 1077-1082.

KRUGLYAK L: 'The use of a genetic map of biallelic markers in linkage studies' NATURE GENETICS, vol. 17, no. 1, 1997, pages 21-24.

SCHORK N J ET AL.: 'Linkage disequilibrium mapping for quantitative traits within case/control settings.' AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 4 Suppl., 1997, page A293.

Section VI

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
EP-A-0 785 280	23.07.1997	28.11.1996	29.11.1995*

* The validity of the claimed priority date has not been checked.

Section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D5 is not mentioned in the description, nor are these documents identified therein.

Section VIII

1. According to the results presented on p.37 (table 3) and the comments on p.46, l.10-11, the determination of the SNP within SEQ ID No. : 301/307 does not seem

to be sufficient to determine whether a patient is at risk of developing - or suffers from- AD. Either the determination of the "haplotype 8" (see fig.7) or the SNP within SEQ ID No. : 304/310 (biallelic marker 99-365/344) seems to be necessary (see p.47, l.1-12). Therefore it would appear that some essential features are missing from **claim 73** (Article 6 taken in combination with Rule 6.3(b) PCT).

2. The method of **claim 55** refers to biallelic markers obtained by the method of claim 1, however the latter are not associated with a trait. Therefore the said claim is not clear (Art. 6 PCT).

3. The expression "known to be located in proximity to one another in the genome" to be found in **several claims** is not clear (Art. 6 PCT) because the term "proximity" is vague and unclear.

4. **Claims 1-72** do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

5. **Claims 1-72** would appear to be not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following: the said claims concern biallelic markers and their use, however the description appears to refer to biallelic markers that consist of SNPs, and the use thereof.

CLAIMS

1. A method of obtaining a plurality of biallelic markers comprising the steps of:

obtaining a nucleic acid library comprising a plurality of genomic DNA fragments comprising the full genome or a portion thereof;

determining the order of said plurality of genomic DNA fragments in the genome;

determining the sequence of selected regions of said plurality of genomic DNA fragments; and

identifying nucleotides in said plurality of genomic DNA fragments which vary between individuals, thereby defining a set of biallelic markers.

2. The method of Claim 1, further comprising selecting a minimally overlapping set of genomic fragments from said nucleic acid library.

3. The method of Claims 1 or 2, further comprising identifying one biallelic marker per genomic DNA fragment.

4. The method of Claims 1 or 2, further comprising identifying two or more biallelic markers per genomic DNA fragment.

5. The method of Claim 1, further comprising detecting a set of biallelic markers having a desired average heterozygosity rate.

6. The method of Claims 1 or 5, further comprising selecting biallelic markers having a heterozygosity rate of at least about 0.18.

7. The method of Claims 1 or 5, further comprising selecting biallelic markers having a heterozygosity rate of at least about 0.32.

8. The method of Claims 1 or 5, further comprising selecting biallelic markers having a heterozygosity rate of at least about 0.42.

9. The method of Claim 1, wherein said identifying step comprises identifying at least about 20,000 biallelic markers.

10. The method of Claim 1, wherein said biallelic markers are separated from one another by an average distance of 10 kb – 200 kb.

11. The method of Claim 1, wherein said biallelic markers are separated from one another by an average distance of 25 kb - 50 kb.

12. The method of Claim 1, wherein the step of determining the sequence of selected regions of said plurality of genomic DNA fragments comprises inserting fragments of said plurality of genomic DNA fragments into a vector to generate a plurality of subclones and

determining the sequence of a region of the inserts in said plurality of subclones or a subset thereof.

13. The method of Claim 12, wherein said step of determining the sequence of a region of said inserts or a subset thereof comprises determining the sequence of one or both end regions of said inserts or a subset thereof.

14. The method of Claim 1, wherein a set of about 10,000 to about 30,000 genomic DNA inserts with an average size between 100 kb and 300 kb are ordered.

15. The method of Claim 1, wherein said identifying step comprises identifying between 1 and 6 biallelic markers per genomic DNA fragment.

16. The method of Claim 1, wherein said identifying step comprises identifying an average of 3 biallelic markers per genomic DNA insert.

17. The method of Claim 1, wherein said genomic DNA fragments are in a Bacterial Artificial Chromosome.

18. The method of Claim 1, further comprising determining the position of said biallelic markers along the genome or a portion thereof.

19. The method of Claim 1, further comprising obtaining pluralities of biallelic markers such that each marker is in linkage disequilibrium with at least one of identified markers.

20. The method of Claim 1, wherein said portion of the genome comprises at least 200 kb of contiguous genomic DNA.

21. The method of Claim 1, wherein said portion of the genome comprises at least 2 Mb of contiguous genomic DNA.

22. The method of Claim 1, wherein said portion of the genome comprises at least 20 Mb of contiguous genomic DNA.

23. The method of Claim 1, further comprising the step of identifying one or more groups of biallelic markers which are in proximity to one another in the genome.

24. The method of Claim 23, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 1 to 5 kb.

25. The method of Claim 23, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 5 kb to 1 Mb.

26. The method of Claim 23, wherein the biallelic markers in each of these groups are located within a genomic region spanning more than 1 Mb.

27. A set of biallelic markers obtained by the method of Claim 1, wherein the markers in said set are on average evenly spaced over the full genome or a portion thereof.

28. The set of biallelic markers of Claim 27, wherein the markers in said set are ordered relative to one another.

29. The set of biallelic markers according to Claim 27 or Claim 28, wherein the markers in said set have a known genomic position.

30. The set of biallelic markers of Claim 27, wherein said biallelic markers are separated from one another by an average distance of 100 to 150 kb.

31. The set of biallelic markers of Claim 27, wherein said biallelic markers are separated from one another by an average distance of 25 to 50 kb.

32. The set of biallelic markers of Claim 27, wherein said biallelic markers are separated from one another by an average distance of 10 to 200 kb.

33. The set of biallelic markers of Claim 27, wherein said biallelic markers have a heterozygosity rate of at least about 0.18.

34. The set of biallelic markers of Claim 27, wherein said biallelic markers have a heterozygosity rate of at least about 0.32.

35. The set of biallelic markers of Claim 27, wherein said biallelic markers have a heterozygosity rate of at least about 0.42.

36. A map comprising an ordered array of at least 20,000 biallelic markers obtained by the method of Claim 1.

37. A method of identifying one or more biallelic markers associated with a detectable trait comprising the steps of:

determining the frequencies of each allele of said one or more biallelic markers obtained by the method of claim 1 in individuals who express said detectable trait and individuals who do not express said detectable trait; and

identifying one or more alleles of said one or more biallelic markers which are statistically associated with the expression of said detectable trait.

38. A method of identifying a haplotype associated with a trait comprising the steps of:

obtaining nucleic acid samples from trait positive and trait negative individuals;

determining the frequencies of the alleles of each member of a group of biallelic markers obtained by the method of claim 1 located in proximity to one another in the genome in said nucleic acid samples; and

identifying a plurality of alleles of biallelic markers having a statistically significant association with said trait.

39. The method of Claim 38, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 1 to 5 kb.

40. The method of Claim 38, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 5 kb to 1 Mb.

41. The method of Claim 38, wherein the biallelic markers in each of these groups are located within a genomic region spanning more than 1 Mb.

42. A method of identifying one or more biallelic markers associated with a detectable trait comprising the steps of:

selecting a gene in which mutations result in a detectable trait or a gene suspected of being associated with a detectable trait; and

identifying one or more biallelic markers obtained by the method of Claim 1 within the genomic region harboring said gene which are associated with said detectable trait.

43. The method of Claim 42, wherein said identifying step comprises:

determining the frequencies of said one or more biallelic markers in individuals who express said detectable trait and individuals who do not express said detectable trait; and

identifying one or more biallelic markers which are statistically associated with the expression of said detectable trait.

44. An array of nucleic acids fixed to a support, said nucleic acids comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, of one or more biallelic markers obtained by the method of Claim 1.

45. An array of nucleic acids fixed to a support, said nucleic acids comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, of one or more groups of biallelic markers obtained by the method of Claim 1 known to be located in proximity to one another in the genome.

46. An array of nucleic acids fixed to a support, said nucleic acids comprising amplification primers for generating an amplification product comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, of one or more groups of biallelic markers obtained by the method of Claim 1 known to be located in proximity to one another in the genome.

47. An array of nucleic acids fixed to a support, said nucleic nucleic acids comprising one or more microsequencing primers for determining the identity of the polymorphic bases of one or more groups of biallelic markers obtained by the method of Claim 1 known to be located in proximity to one another in the genome.

48. An array of nucleic acids fixed to a support, wherein said nucleic acids are complementary to one or more microsequencing primers for determining the identities of the polymorphic bases of one or more biallelic markers obtained by the method of Claim 1 known to be located in proximity to one another in the genome.

49. The array of any one of Claims 45 to 48, wherein the members of each of said one or more groups of biallelic markers are located in physical proximity to one another on said support.

50. The array of any one of Claims 45 to 48, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 1 to 5 kb.

51. The array of any one of Claims 45 to 48, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 5 kb to 1 Mb.

52. The array of any one of Claims 45 to 48, wherein the biallelic markers in each of these groups are located within a genomic region spanning more than 1 Mb.

53. The array of any one of Claims 45 to 48, wherein each group of biallelic markers comprises at least 3 biallelic markers.

54. The array of any one of Claims 45 to 48, wherein each group of biallelic markers comprises at least 20 biallelic markers.

55. A method for determining whether an individual is at risk of developing a detectable trait or suffers from a detectable trait associated with said trait comprising the steps of:

obtaining a nucleic acid sample from said individual;

screening said nucleic acid sample with one or more biallelic markers obtained by the method of Claim 1; and

determining whether said nucleic acid sample contains one or more of biallelic markers statistically associated with said detectable trait.

56. The method of Claim 55, wherein said biallelic markers were obtained by the method of Claim 37.

57. The method of Claim 55, wherein said biallelic markers were obtained by the method of Claim 42.

58. A method of using a drug comprising:

obtaining a nucleic acid sample from an individual;

determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 1 which is associated with a positive response to treatment with said drug or one or more biallelic markers obtained by the method of Claim 1 which is associated with a negative response to treatment with said drug; and

administering said drug to said individual if said nucleic acid sample contains one or more biallelic markers associated with a positive response to treatment with said drug or if said nucleic acid sample lacks one or more biallelic markers associated with a negative response to said drug.

59. The method of Claim 58, wherein said determining step comprises determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 37 which is associated with a positive response to treatment with said drug or one or more biallelic markers obtained by the method of Claim 37 which is associated with a negative response to treatment with said drug.

60. The method of Claim 58, wherein said determining step comprises determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 42 which is associated with a positive response to treatment with said drug or one or more biallelic markers obtained by the method of Claim 42 which is associated with a negative response to treatment with said drug.

61. A method of selecting an individual for inclusion in a clinical trial of a drug comprising:

obtaining a nucleic acid sample from an individual;

determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 1 which is associated with a positive response to treatment with said drug or one or more biallelic markers associated with a negative response to treatment with said drug in said nucleic acid sample; and

including said individual in said clinical trial if said nucleic acid sample contains one or more biallelic markers obtained by the method of Claim 1 which is associated with a positive response to treatment with said drug or if said nucleic acid sample lacks one or more biallelic markers associated with a negative response to said drug.

62. The method of Claim 61, wherein said determining step comprises determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 37 which is associated with a positive response to treatment with said drug or one or more biallelic markers obtained by the method of Claim 37 which is associated with a negative response to treatment with said drug.

63. The method of Claim 61, wherein said determining step comprises determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 42 which is associated with a positive response to treatment with said drug or one or more biallelic markers obtained by the method of Claim 42 which is associated with a negative response to treatment with said drug.

64. A method of identifying a gene associated with a detectable trait comprising the steps of:

determining the frequency of each allele of one or more biallelic markers obtained by the method of Claim 1 in individuals having said detectable trait and individuals lacking said detectable trait;

identifying one or more alleles of one or more biallelic markers having a statistically significant association with said detectable trait; and

identifying a gene in linkage disequilibrium with said one or more alleles.

65. The method of Claim 64, further comprising identifying a mutation in the gene which is associated with said detectable trait.

66. A method of identifying a gene associated with a detectable trait comprising:

selecting a gene suspected of being associated with a detectable trait; and

identifying one or more biallelic markers obtained by the method of Claim 1 within the genomic region harboring said gene which are associated with said detectable trait.

67. The method of any one of Claims 37, 38, 42, 55, 64 or 66, wherein said detectable trait is selected from the group consisting of disease, drug response, drug efficacy, and drug toxicity.

68. The method of Claim 66, wherein said identifying step comprises:

determining the frequencies of said one or more biallelic markers in individuals who express said detectable trait and individuals who do not express said detectable trait; and

identifying one or more biallelic markers which are statistically associated with the expression of said detectable trait.

69. A method of identifying a haplotype associated with a trait comprising the steps of:

obtaining nucleic acid samples from trait positive and trait negative individuals;

conducting an amplification reaction on said nucleic acid samples using amplification primers capable of generating amplification products containing the polymorphic bases of a plurality of biallelic markers;

contacting one or more arrays of nucleic acids fixed to a support with said amplification products, wherein said nucleic acids fixed to a support comprise at least 8 consecutive nucleotides, including the polymorphic nucleotide, of one or more groups of biallelic markers obtained by the method of Claim 1 known to be located in proximity to one another in the genome;

determining the identities of the polymorphic bases of said amplification products; and

identifying a haplotype having a statistically significant association with said trait.

70. A method of identifying a haplotype associated with a trait comprising the steps of:

obtaining nucleic acid samples from trait positive and trait negative individuals;

conducting amplification reactions on said nucleic acid samples using amplification primers capable of generating amplification products containing the polymorphic bases of a plurality of biallelic markers;

contacting one or more arrays of nucleic acids fixed to a support with said amplification products, wherein said nucleic nucleic acids fixed to a support comprise one or more microsequencing primers for determining the identity of the polymorphic bases of one or more groups of biallelic markers obtained by the method of Claim 1 known to be located in proximity to one another in the genome;

conducting microsequencing reactions on said amplification products using microsequencing primers on said arrays, thereby generating elongated microsequencing primers comprising the polymorphic bases of said amplification products;

determining the identities of said polymorphic bases; and

identifying a haplotype having a statistically significant association with said trait.

71. A method of identifying a haplotype associated with a trait comprising the steps of:

obtaining nucleic acid samples from trait positive and trait negative individuals;

conducting amplification reactions on said nucleic acid samples using amplification primers which are capable of generating amplification products containing the polymorphic bases of a plurality of biallelic markers;

conducting microsequencing reactions on said nucleic acid samples, thereby generating microsequencing products containing the polymorphic bases of one or more biallelic markers at their 3' ends, said polymorphic bases being detectably labeled;

contacting one or more arrays according to Claim 48 with said microsequencing products such that said microsequencing products specifically hybridize to said nucleic acids complementary to said microsequencing primers;

determining the identities of the polymorphic bases of said microsequencing products; and

identifying a haplotype having a statistically significant association with said trait.

72. A method of identifying a haplotype associated with a trait comprising the steps of:

obtaining nucleic acid samples from trait positive and trait negative individuals;

contacting one or more arrays of nucleic acids fixed to a support with said nucleic acid sample, wherein said nucleic acids fixed to a support comprise amplification primers for generating an amplification product comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, of one or more groups of biallelic markers obtained by the method of Claim 1 known to be located in proximity to one another in the genome;

conducting an amplification reaction on said nucleic acid samples using amplification primers on said array which are capable of generating amplification products containing the polymorphic bases of a plurality of biallelic markers;

determining the identities of the polymorphic bases of said amplification products; and

identifying a haplotype having a statistically significant association with said trait.

73. A method of determining whether an individual is at risk of developing Alzheimer's disease or whether the individual suffers from Alzheimer's disease as a result of possessing the Apo E ∈4 Site A allele comprising:

obtaining a nucleic acid sample from said individual; and

determining the identity of the polymorphic base in one or more of the sequences selected from the group consisting of SEQ ID Nos. 301-305 and SEQ ID Nos. 307-311 or the sequences complementary thereto in said nucleic acid sample.

74. The method of Claim 73, further comprising determining whether said nucleic acid sample contains the sequence of SEQ ID No. 306 or the sequence complementary thereto.

75. The method of Claim 73, wherein said step of determining the identity of the polymorphic bases in one or more of the sequences selected from the group consisting of SEQ ID Nos. 301-305 and SEQ ID Nos. 307-311 or the sequences complementary thereto comprises determining whether said nucleic acid sample contains the sequence of SEQ ID No. 311 or the sequence complementary thereto.

76. The method of Claim 75, further comprising determining whether said nucleic acid sample contains the sequence of SEQ ID No. 306 or the sequence complementary thereto.

77. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID No. 301, SEQ ID No. 307, the sequences complementary thereto, and fragments comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, thereof.

78. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID No. 302, SEQ ID No. 308, the sequences complementary thereto, and fragments comprising at least 8 consecutive nucleotides thereof.

79. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID No. 303, SEQ ID No. 309, the sequences complementary thereto, and fragments comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, thereof.

80. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID No. 304, SEQ ID No. 310, the sequences complementary thereto, and fragments comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, thereof.

81. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID No. 305, SEQ ID No. 311, the sequences complementary thereto, and fragments comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, thereof.

82. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID Nos. 313-317, SEQ ID Nos. 319-323, and fragments comprising at least 8 consecutive nucleotides thereof.

83. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID Nos. 325-329, SEQ ID Nos. 331-335, the sequence complementary thereto, and fragments comprising at least 8 consecutive nucleotides thereof.

84. A set of nucleic acids comprising amplification primers for generating an amplification product comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, of one or more biallelic markers obtained by the method of Claim 1.

85. A set of nucleic acids comprising one or more microsequencing primers for determining the identity of the polymorphic base of one or more nucleic acids comprising at least 8 consecutive nucleotides, including the polymorphic nucleotide, of one or more biallelic markers obtained by the method of Claim 1.